REMARKS

In the Office Action dated December 10, 2002, the Examiner rejected Claims 1, 2, 6 and 7 under 35 U.S.C. § 103(a) as being unpatentable over Nutter et al. (WO 98/11883) in view of Todd et al. (U.S. Patent 5,082,975), and Claims 3-5 and 12-14 under 35 U.S.C. § 103(a) as being unpatentable over Nutter et al. in view of Todd et al. and Lefren et al. (U.S. Patent No. 4,431,427). The Examiner also objected to Claim 8 as being dependent upon a rejected claim.

The Examiner's rejection of each of Claims 1-7 and 12-14 is based on two assertions not supported by the references cited. In the first instance, the Examiner suggests that Nutter et al. teaches the administration of hexahydrocolupulone (HHC) at a concentration of 0.2 to 62.5 ppm. In the second instance, the Examiner suggests that Todd et al. teaches that the administration of HHC at a concentration of between 0.2 and 25 ppm will lessen the inhibition of lactobacilli, thus allowing lactobacillus to grow. The Applicants respectfully submit that in each of these instances the cited references fail to support the Examiner's conclusions.

Although Nutter et al. makes reference to the use of HHC in topical applications, it fails to provide any guidance as to the concentration at which HHC should be applied. In fact, the guidance provided is more appropriate for administration of HHC either by parenteral administration (e.g., by injection) or by oral ingestion. For example, Nutter et al. indicates that a suitable dose of HHC should be in the range of about 0.5 to about 100 mg per kilogram of body weight of the recipient per day, and should be administered in unit dosage form. (Page 11, line 26 to page 12, line 3, emphasis added.) Nutter et al. also indicates that HHC should be administered so as to achieve a peak plasma concentration level of about 0.5 to 75 μM, and suggests the use of continuous infusion to maintain the desirable amount of

HHC in the blood system. (Page 12, lines 4-12.) Nowhere does Nutter et al. suggest or teach the concentrations at which HHC should be applied in topical applications.

It must be recognized that there exists a substantial difference in the application environment when a compound is administered topically versus parenterally. Factors such as the pH and microbial flora of the environment, as well as the ability of the compound to be washed away or to evaporate, may have a substantial impact on the effectiveness of the compound, thus requiring variations in the manner and concentration at which the compound is applied. For example, the vaginal area typically provides an acidic environment with a broad microbial flora. Some compounds or compound concentrations may prove ineffective in this environment if they exhibit a lack of stability in acidic conditions. Other compounds or compound concentrations may prove ineffective or provide additional deleterious effects by disrupting the vaginal area's natural microbial flora. In this latter case, one concern would be the application of a compound at a concentration that ultimately results in the disruption of the natural flora to the point that other undesired microorganisms are allowed to grow and proliferate.

Accordingly, the administration of a compound at a concentration designated for parenteral application does not necessarily correlate with the concentration at which the compound should be administered during a topical application. Therefore, the concentration at which the compounds of the present invention should be administered to be effective in topical applications, and especially in vaginal applications, would not have been obvious to one of ordinary skill in the art when such individual only had access to concentrations for parenteral applications. For this reason alone, the Applicants respectfully submit that the rejection of Claims 1-7 and 12-14 and the objection of Claim 8 should be withdrawn. To clarify this point, the Applicants have amended Claim 1 to indicate that the claimed

compounds are administered as a topical application. The Applicants have also added new Claims 15-25 addressing the administration of the compounds to the vaginal area.

The Examiner's rejection is also based on the supposition that Todd et al. teaches that HHC concentration levels below 50 ppm would lessen the inhibitory effect of HHC on lactobacilli, thus allowing the lactobacilli to grow. However, this assertion is not supported by Todd et al. as the reference does not state anywhere that HHC concentration levels below 50 ppm will lessen the inhibitory effect of HHC on lactobacilli, and hindsight created by the present application should not be used to support such a conclusion. The Todd et al. reference should be reviewed for what it teaches, and it teaches only that lactobacillus may be killed at concentration levels above 50 ppm.

The Examiner infers from the fact that Todd et al. describes the use of HHC at concentrations greater than 50 ppm to suggest that concentrations below 50 ppm would not inhibit the growth of lactobacilli. However, this inference is neither supported by Todd et al. nor by any other evidence provided by the Examiner. Instead, the Examiner relies upon an argument of logic and the present application. However, the logic is fundamentally flawed as it presumes that HHC will not inhibit lactobacilli growth at concentrations below 50 ppm because Todd et al. only describes lactobacilli inhibition at concentrations greater than 50 ppm. The problem is that Todd et al. does not report any experiments being conducted at concentrations below 50 ppm and therefore provides no guidance whatsoever as to whether and at what concentrations below 50 ppm will HHC stop inhibiting lactobacilli growth and proliferation. In the absence of any evidence to the contrary, one of ordinary skill in the art could readily believe that concentrations as low as 0.2 ppm could also be effective in preventing the growth of lactobacillus. As a result, Todd et al. should not be offered for the premise that it would have been obvious to one of ordinary skill in the art to employ HHC concentration levels below 50 ppm, and more particular in the range of 0.2-25 ppm, to lessen

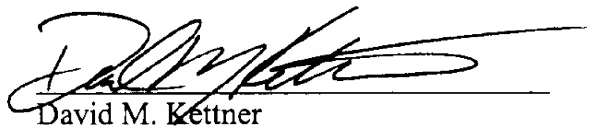
the inhibitory effect of HHC on lactobacilli, thus allowing lactobacillus to grow. For this reason, the Applicants respectfully submit that the rejection of Claims 1-7 and 12-14 and the objection of Claim 8 should be withdrawn.

Finally, neither Todd et al. nor Nutter et al. suggest or teach the administration of the compounds of the present invention to the vaginal area. As indicated above, the normal bacterial flora found in the vaginal area is generally sensitive to major disruptions. The most common effect of such disruptions is the onset of bacterial infections, such as yeast infections caused by excessive proliferation of *Candida albican*. To avoid such disruptions, one must strike a balance between the compounds and concentrations that inhibit the growth of the undesired bacterium and the use of compounds and concentrations that disrupt the natural flora of the application environment. One must also take into consideration the pH levels of the vaginal area and the likelihood that the applied compounds could be washed away or diluted. The experiments and data provided by Todd et al. and Nutter et al., whether combined or standing alone, fail to consider these factors or provide any guidance to achieve the necessary balance to provide treatment solutions for application to the vaginal area. In the absence of such information, it would not have been obvious to one of ordinary skill in the art to administer the compounds of the present invention to the vaginal area in the range of 0.2 to 25 ppm in order to effectively inhibit the growth of *S. aureus* without preventing the growth of lactobacillus. For this reason, the Applicants respectfully submit that the rejection of Claims 1-7 and 12-14 and the objection of Claim 8 should be withdrawn.

The Applicants therefore respectfully submit that Claims 1-8 and 12-25 are in a condition for allowance, and request reconsideration of the merits of this application. No fee is believed due in connection with this response, however, should any fee be due, please charge the fee to Deposit Account No. 17-0055. Should any extension of time be due in this

or any subsequent response, please consider this a request for the appropriate extension of time and a request to charge any fee due in that regard to the same deposit account.

Respectfully submitted,



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